DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 357

[Docket No. 87N-0181]

Cholecystokinetic Drug Products for Over-the-Counter Human Use; Proposed Amendment of Final Monograph

AGENCY: Food and Drug Administration.
ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that would amend the final monograph for over-the-counter (OTC) cholecystokinetic drug products to include the ingredient hydrogenated soybean oil. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATE: Written comments or objections by October 14, 1988.

ADDRESS: Written comments or objections to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of June 10, 1983 (48 FR 27004), FDA issued a final monograph for OTC cholecystokinetic drug products (21 CFR Part 357, Subpart C). The only active ingredient included in the monograph was a 50-percent aqueous emulsion of corn oil.

On March 16, 1984, FDA received a citizen petition (Docket No. 79N-0368/CP) requesting that the final monograph for OTC cholecystokinetic drug products be amended to include a powder dosage form containing hydrogenated soybean oil and lecithin. The citizen petition was supplemented by data contained in letters dated January 14, 1985, November 14, 1985, June 1, 1987, and January 13, 1988. These letters are on file in Docket No. 79N-0368 as LET004, LET006, LET009, and LET011, respectively.

After reviewing the citizen petition and the supplemental data, the agency concludes that there is sufficient evidence to generally recognize hydrogenated soybean oil as safe and effective and not misbranded for use as an OTC cholecystokinetic drug product. The citizen petition contained the results of a study designed to compare the effectiveness of two contrast agents at two different dosage levels both without and with a fatty meal (consisting of 12.4 grams (g) of hydrogenated soybean oil) prior to ingestion of the contrast agent. Although specific data on gallbladder contraction were not provided, the study results did indicate that of the subjects who received the hydrogenated soybean oil product, 40 percent (134 visualizations recorded in a total of 330 examinations) had the cystic duct visualized upon radiographic examination. The agency concludes that the submitted data are adequate to demonstrate the effectiveness of hydrogenated soybean oil in producing gallbladder contraction.

Information provided in the supplemental data indicates that the role of lecithin in the product is as an inactive ingredient. The information also indicates that lecithin and the other inactive ingredients would not contribute significantly to the cholecystokinetic effect of the product. Additionally, FDA was informed by the petitioner that the hydrogenated soybean oil contained in the product was food-grade, partially-hydrolyzed soybean oil with a melting point of 41 to 43.5 °C, an iodine value of 65 to 69, and a fatty acid composition as follows (Ref. 1):

Fatty acid	Percent composition
Myristic acid	0.1
Palmitic acid	10.0
Palmitoleic acid	.1
Stearic acid	13.5
Oleic acid	72.0
Linoleic acid	3.8
Linolenic acid	.1
Arachidic acid	.5
Behenic acid	.2

Hydrogenation of vegetable oils is a chemical reaction consisting of addition of hydrogen at double bonds of unsaturated acyl groups. This process results in a decreased susceptibility of oils to oxidative deterioration (Ref. 2). Corn oil and hydrogenated soybean oil have a similar high content of long chain triglycerides of fatty acids, e.g., oleic acid, linoleic acid, palmitic acid, and stearic acid (Refs. 2, 3, and 4). Although it has long been generally known that gallbladder contraction occurs in response to a fatty meal (Refs. 5, 6, and 7), recent data suggest that the ingestion of long-chain triglycerides of fatty acids initiates gallbladder contraction. Two studies, in which the effect of medium-chain triglycerides and long-chain triglycerides of fatty acids on gallbladder contraction were compared, demonstrated that patients responded with normal and vigorous gallbladder contraction after ingesting a meal of long-chain triglycerides of fatty acids whereas no significant response was observed after ingestion of medium-chain triglycerides of fatty acids (Refs. 8 and 9). Because the long-chain triglyceride content of corn oil and soybean oil as described above is similar, the effect on gallbladder contraction is also similar.

Accordingly, the agency is proposing to amend the final monograph on OTC cholecystokinetic drug products to include hydrogenated soybean oil as described above as an active ingredient. The agency proposes that the statement of identity and indications for products containing this ingredient follow § 357.250 (a) and (b) of the cholecystokinetic final monograph. The agency is also proposing that the directions section of the monograph (21 CFR 357.250(d)(3)) be modified to include the following: Oral dosage is 12.4 grams hydrogenated soybean oil in a suitable, water-dispersible powder in 2 to 3 ounces of water. Stir briskly to prepare a suspension before using. Drink 20 minutes before diagnostic gallbladder x-ray or as directed by a doctor.

The agency is aware that the hydrogenated soybean oil product covered by the petition is currently being marketed as a prescription drug. Although the agency is proposing in this notice to switch hydrogenated soybean oil to OTC use from its present status as a prescription drug, OTC marketing may not begin at this time. In the **Federal Register** of June 3, 1983 (48 FR 24925), FDA explained the enforcement policy for drugs that were originally on prescription status but which were being proposed for OTC marketing under the OTC drug review. As noted there, 21 CFR 330.13 permits OTC marketing of a drug previously limited to prescription use prior to publication of a final monograph provided that certain conditions are met. To qualify for such status, the drug must, at a minimum, have been considered by an OTC drug advisory review panel and either been recommended for OTC marketing by the panel or subsequently determined by FDA to be suitable for OTC marketing. Hydrogenated soybean oil was not considered by a panel and, therefore, does not qualify for early OTC marketing under the terms of the enforcement policy set out in § 330.13. FDA believes that public comments submitted in response to the proposed switch in status should be evaluated before a final agency decision on OTC status is made and before OTC marketing begins. Accordingly, until such comments are reviewed,

hydrogenated soybean oil will remain a prescription drug.

References

(1) Letter from Richard A. Sosin, Summit Medical Products, Inc., to Dr. William E. Gilbertson, January 13, 1988, coded LET011, Docket No. 79N–0368, Dockets Management Branch.

(2) DeMan, J.M., "Principles of Food Chemistry," AVI Publishing Company, Inc., Westport, CT, pp. 35–85, 1976.

(3) Windholz, M., editor, "The Merck Index," 10th Ed., Merck and Co., Rahway, NJ, p. 361 and 1249, 1983.

(4) Tyler, V.E., L.R. Brady, and J.E. Robbers, "Pharmacognosy," 8th Ed., Lea and Febiger, Philadelphia, 1981.

(5) Wiener, I., et al., "Release of Cholecystokinin in Man. Correlation of Blood Levels With Gallbladder Contraction," *Annals of Surgery*, 194:321–325, 1981.

(6) Bobba, V.R., et al., "Gallbladder Dynamics Induced by a Fatty Meal in Normal Subjects and Patients With Gallstones; Concise Communication," *Journal of Nuclear Medicine*, 25:21–24, 1984.

(7) Upp, J.R., Jr., et al., "Correlation of Cholecystokinin Receptors With Gallbladder Contractility in Patients With Gallstones," *Annals of Surgery*, 205:641–648, 1987.

(8) Ladas, S.D., et al., "Comparison of the Effects of Medium and Long Chain Triglyceride Containing Liquid Meals on Gallbladder and Small Intestinal Function in Normal Man," *Gut*, 25:405–411, 1984.

(9) Isaacs, P.E.T., et al., "Comparison of Effects of Ingested Medium- and Long-Chain Triglyceride on Gallbladder Volume and Release of Cholecystokinin and Other Gut Peptides," *Digestive Diseases and Sciences*, 32:481–486, 1987.

The agency advises that any final rule resulting from this proposed rule will be effective 12 months after its date of publication in the **Federal Register**. On or after that date, any OTC drug product that is not in compliance may not be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to the rule that is repackaged or relabeled after the effective date of the rule must be in compliance with the rule regardless of the date that the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the rule at the earliest possible date.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC cholecystokinetic drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96–354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC cholecystokinetic drug products is not expected to pose such an effect on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC cholecystokinetic drug products. Comments regarding the impact of this rulemaking on OTC cholecystokinetic drug products should be accompanied by appropriate documentation.

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday. This action was considered under FDA's final rule implementing the National Environmental Policy Act (21 CFR Part 25).

Interested persons may, on or before October 14, 1988, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments or objections. Three copies of all comments or objections are to be submitted, except that individuals may submit one copy. Comments and objections are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments and objections may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 357

Cholecystokinetic drug products, Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 357 as follows:

PART 357—MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR Part 357 is revised to read as follows:

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

2. Section 357.210 is revised to read as follows:

§ 357.210 Cholecystokinetic active ingredients.

The active ingredient of the product consists of any of the following when used within the specified concentration and dosage form established for each ingredient:

(a) 50-percent aqueous emulsion of corn oil.

(b) Hydrogenated soybean oil in a suitable, water-dispersible powder. The hydrogenated soybean oil is food-grade, partially hydrolyzed with a melting point of 41 to 43.5 °C, an iodine value of 65 to 69, and a fatty acid composition as follows:

Fatty acid	Percent composition
Myristic acid	0.1
Palmitic acid	10.0
Palmitoleic acid	.1
Stearic acid	13.5
Oleic acid	72.0
Linoleic acid	3.8
Linolenic acid	.1
Arachidic acid	.5
Behenic acid	.2

3. In § 357.250, paragraphs (d) (2) and (3) are revised to read as follows:

§ 357.250 Labeling of cholecystokinetic drug products.

* * * * *

(d) * * *

(2) *For products containing 50-percent aqueous emulsion of corn oil.*

(i) "Shake well before using."

(ii) Oral dosage is 60 milliliters 20 minutes before diagnostic gallbladder x-ray or as directed by a doctor.

(3) *For products containing hydrogenated soybean oil.* Oral dosage is 12.4 grams in a suitable, water-dispersible powder in 2 to 3 ounces of water. Stir briskly to prepare a suspension before using. Drink 20 minutes before diagnostic gallbladder x-ray or as directed by a doctor.

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4. Section 357.280 is revised to read as follows:

§ 357.280 Professional labeling.

The labeling provided to health professionals (but not to the general public) may contain the following information for ingredients identified in § 357.210: *Indication.* "For visualization of biliary ducts during cholecystography."

Dated: June 6, 1988.

Frank E. Young,

Commissioner of Food and Drugs.

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